Acid-Base Disorders in the Critically Ill Patient

Anand Achanti and *Harold M. Szerlip*

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

Abstract

Acid-base disorders are common in the intensive care unit. By utilizing a systematic approach to their diagnosis, it is easy to identify both simple and mixed disturbances. These disorders are divided into four major categories: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. Metabolic acidosis is subdivided into anion gap and non–gap acidosis. Distinguishing between these is helpful in establishing the cause of the acidosis. Anion gap acidosis, caused by the accumulation of organic anions from sepsis, diabetes, alcohol use, and numerous drugs and toxins, is usually present on admission to the intensive care unit. Lactic acidosis from decreased delivery or utilization of oxygen is associated with increased mortality. This is likely secondary to the disease process, as opposed to the degree of acidemia. Treatment of an anion gap acidosis is aimed at the underlying disease or removal of the toxin. The use of therapy to normalize the pH is controversial. Non–gap acidoses result from disorders of renal tubular H^+ transport, decreased renal ammonia secretion, gastrointestinal and kidney losses of bicarbonate, dilution of serum bicarbonate from excessive intravenous fluid administration, or addition of hydrochloric acid. Metabolic alkalosis is the most common acid-base disorder found in patients who are critically ill, and most often occurs after admission to the intensive care unit. Its etiology is most often secondary to the aggressive therapeutic interventions used to treat shock, acidemia, volume overload, severe coagulopathy, respiratory failure, and AKI. Treatment consists of volume resuscitation and repletion of potassium deficits. Aggressive lowering of the pH is usually not necessary. Respiratory disorders are caused by either decreased or increased minute ventilation. The use of permissive hypercapnia to prevent barotrauma has become the standard of care. The use of bicarbonate to correct the acidemia is not recommended. In patients at the extreme, the use of extracorporeal therapies to remove CO_2 can be considered.

CJASN 18: 102–112, 2023. doi: https://doi.org/10.2215/CJN.04500422

Internal Medicine/ Nephrology, Medical University of South Carolina, Charleston, South Carolina

Correspondence: Dr. Harold M. Szerlip, Division of Nephrology, 822 CSB, Medical University of South Carolina, 96 Jonathan Lucas Street, Charleston, SC 29425. Email: Szerlip@musc.edu

Introduction

Because of the very nature of critical illness, nephrologists seeing patients in the intensive care unit (ICU) frequently encounter a variety of acid-base disorders. Sepsis, diabetes, kidney failure, drug overdoses, hepatic dysfunction, and compromised respiratory function all disturb the body's ability to defend pH and maintain homeostasis. In addition, the therapeutic interventions used in the intensive care setting further derange acid-base balance. Changes in blood pH in either direction are associated with higher mortality (1). Therefore, the ability to identify these acid-base disorders, understand the underlying pathophysiology, and provide appropriate therapy is paramount to the care of patients who are critically ill.

Normal blood pH is between 7.36 and 7.44, which corresponds to a hydrogen ion concentration of 44–36 nmol/L. When pH is <7.36, an acidemia is present, whereas when it is >7.44 an alkalemia exists. It needs to be stressed, however, that because multiple acid-base disorders can exist simultaneously, the pH may be in the normal range. Therefore, the clinician needs to follow a systematic approach to identify the underlying disorders.

There are two competing approaches to the diagnosis of acid-base disorders: the classic Henderson–Hasselbalch method using carbonic acid/bicarbonate as the conjugate acid-base pair and the strong-ion difference, as advocated by Stewart (2). Although many intensivists have gravitated toward the Stewart method, there is no advantage to utilizing this more complicated approach (3,4). The classic approach to acid-base divides the disorders into four categories: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. A comprehensive review of acid-base homeostasis and the myriad causes of acid-base disorders is beyond the scope of this review, which focuses on those disorders that occur in the critically ill for which a nephrologist is most often consulted.

Approach to Acid-Base Disorders

Although it is often said that understanding acid-base disorders is complicated, if approached in a systematic fashion, it becomes quite simple. Five basic steps should be followed in all patients (Figure 1).

(1) Perform a thorough history and physical to obtain clues pointing to an acid-base disturbance.
(2) Obtain a blood gas analysis. This will indicate if there is an acidemia or alkalemia, and whether it is metabolic or respiratory. If the patient is hemodynamically stable because there are minimal differences between arterial and venous specimens, either one can be utilized (5,6). In patients in

 Copyright © 2022 by the American Society of Nephrology

SHOUT
SHARE
IT

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

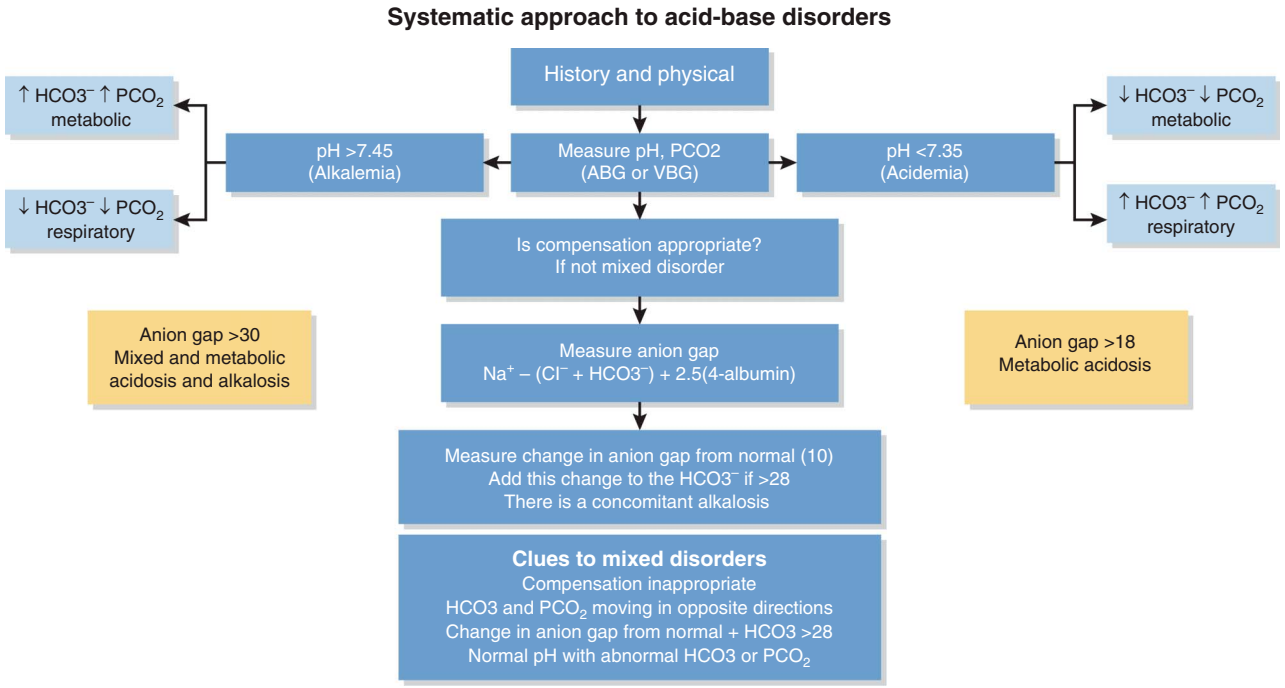

Figure 1. | **A systematic approach to acid-base disorders**.

shock, however, we recommend using an arterial specimen. If the pCO_2 and the HCO_3 are moving in the same direction, there is usually a single disturbance. If they are moving in opposite directions, there is a mixed disturbance or laboratory error.

(3) Determine whether compensation is appropriate (Table 1). Remember compensation almost never returns the pH to normal.

(4) No matter what the pH, always calculate the anion gap (AG)=Na − (Cl + TCO_2). Note that the calculation of the AG uses the TCO_2 obtained from the chemistry panel. This includes HCO3, carbonate, and dissolved CO_2 and is usually 2 meq greater than the HCO_3 calculated on the ABG (Figure 2). Because the major unmeasured anion is albumin, it is important to correct for hypoalbuminemia. For every 1 g/dl decrease in albumin from normal, add 2.5 to the AG (7). An AG >18, regardless of pH, almost always indicates the presence of an organic acid (the retention of sulfates and phosphates that occur with markedly depressed kidney function will increase the AG but rarely will it be >18). Because of differences in each individual's AG and the fact that the normal values for electrolytes vary between laboratories, a normal AG is between 6 and 12 meq/L. For practical purposes, 10 meq/L can be considered the normal gap.

(5) Assuming that the proton space and the bicarbonate space are approximately equivalent, then for every 1 meq/L increase in the AG, there should be a 1 meq/L decrease in the TCO_2. To determine whether the decrease in TCO_2 is equal to the increase in AG above normal, add the increase in AG above normal to the TCO_2. This will determine what the TCO_2 would have been if there were not an elevated AG. If >28 meq/L, there is likely a concurrent metabolic alkalosis. An AG >30 (delta gap >20) almost always indicates an underlying metabolic alkalosis.

Metabolic Acidosis

Metabolic acidosis is extremely common in the ICU and often is present on admission. It results from either an overproduction or decreased elimination of acid, or from a loss of base. Although a simple metabolic acidosis will lower the pH, depending on whether there are other

Table 1. Expected compensation for acid-base disorders

Disorder	Expected Compensation
Metabolic acidosis	PCO_2=HCO_3+15 PCO_2=1.5 x HCO_3+8 ± 2
Metabolic alkalosis	PCO_2 ↑ by 0.5–0.7 for each 1 meq ↑ HCO_3
Acute respiratory acidosis	1 meq ↑ in HCO_3 for every 10 mm Hg ↑PCO_2
Chronic respiratory acidosis	3.5 meq ↑ in HCO_3 for every 10 mm Hg ↑PCO_2
Acute respiratory alkalosis	2 meq ↓ in HCO_3 for every 10 mm Hg ↓ in PCO_2
Chronic respiratory alkalosis	5 meq ↓ in HCO_3 for every 10 mm Hg ↓ in PCO_2

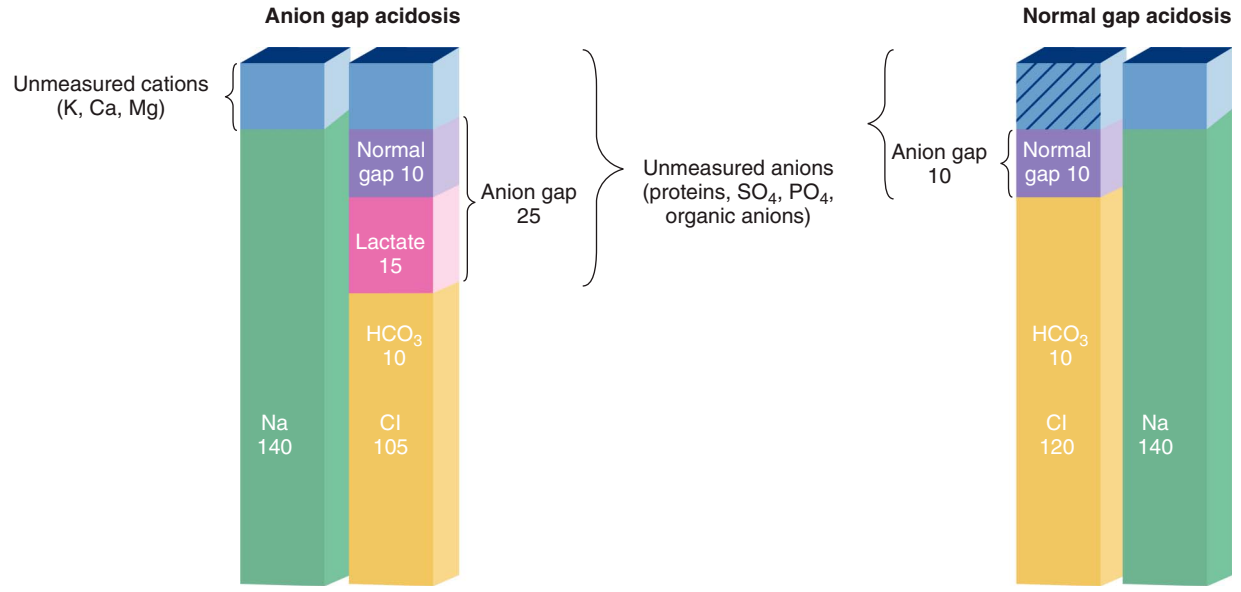

Figure 2. | **Because the concentration of unmeasured anions, predominantly albumin, is greater than that of unmeasured cations, there is an anion gap (AG) ($Na^+ - [Cl^- + HCO3^-]$) between 8 and 10 meq/L.** The addition of an organic anion (*i.e.*, lactate, β-hydroxybutyrate) increases the AG. However, when Cl^- is the anion that accompanies H^+, there is no change in the AG.

acid-base disorders, the pH may be normal or even elevated. Metabolic acidosis can be further divided into high AG metabolic acidosis and normal AG metabolic acidosis (Figures 2 and 3). Distinguishing between these two disorders is helpful in establishing the cause of the acidosis.

AG Metabolic Acidosis

AG metabolic acidosis results from a buildup of unmeasured organic acids. Increases in AG >18 are clinically significant, although the unmeasured anion may not always be identified (8). The greater the AG, the more likely the cause can be determined (8). The differential for an AG acidosis can be remembered using the mnemonic GOLDMARK (9) (Table 2). We will briefly review the major causes of AG acidosis most prevalent in the ICU.

L-Lactic Acidosis. L-lactic acidosis is defined by a L-lactate level of >4 mmol/L. L-lactic acidosis is the most common metabolic acidosis in patients who are critically ill, and there is a strong correlation between the rise in lactate and mortality (10,11). Because the AG, even when corrected for hypoalbuminemia, is a poor predictor of lactate levels, it is important that lactate be directly measured (12–14). Elevated lactate levels can occur due to increased production or decreased clearance (Figure 4). Lactic acidosis is divided into type A, which occurs when there is decreased oxygen delivery to tissues from severe hypoxemia or decreased perfusion, and type B due to impaired mitochondrial function (Table 3). The sources of lactic acidosis in the ICU are numerous, including increased metabolism, tissue ischemia, the use of catecholamines, and a wide variety of other medications.

An important cause of lactic acidosis that occurs in the ICU and may not be recognized by the clinician is thiamine deficiency (15). Thiamine deficiency can occur due to

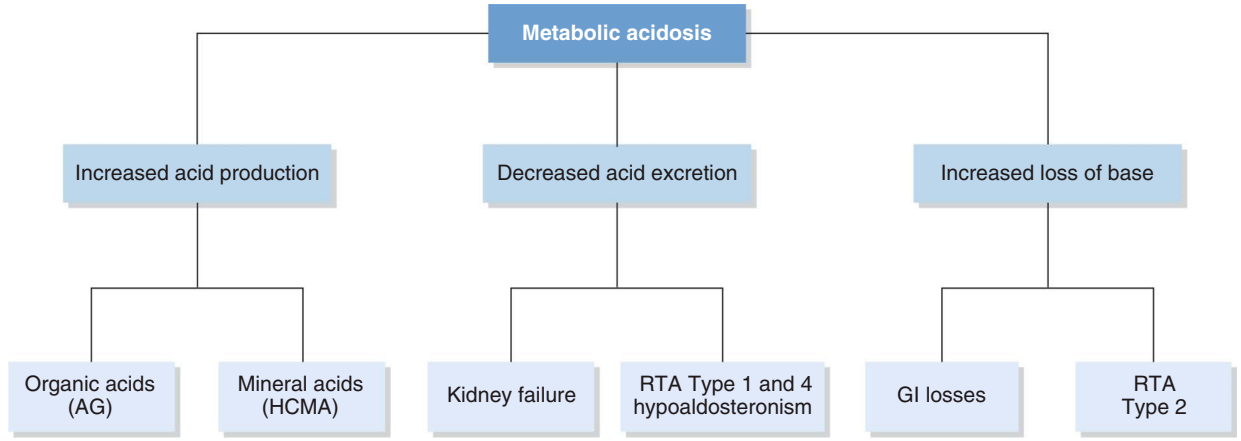

Figure 3. | **Etiology of metabolic acidosis.** HCMA, hyperchloremic metabolic acidosis; RTA, renal tubular acidosis.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

Table 2. Mnemonic for causes of anion gap acidosis (9)

Letter	Meaning
G	Glycols
O	Oxyproline (pyroglutamic acid)
L	L-lactate
D	D-lactate
M	Methanol
A	Acetylsalicylic acid
R	Renal failure
K	Ketoacidosis

Table 3. Causes of lactic acidosis

Type A	Type B
Decreased oxygen delivery	Impaired oxygen utilization or defective lactate metabolism
Systemic hypoperfusion	Underlying disease
Shock	Liver failure
Sepsis	Kidney failure
	Malignancy
	Sepsis
	Pheochromocytoma
	Thiamine deficiency
	Diabetic ketoacidosis
	Alkalosis
Local hypoperfusion	Drugs/toxins
Thrombus/emboli	Acetaminophen
Volvulus/torsion	Salicylate
Compartment syndrome	Metformin
Sepsis	Catecholamines
	HARRT (first generation)
	Linezolid
	Propofol
	Cocaine
Profound hypoxia	Congenital metabolic defects
ARDS, COPD, asthma	
Carbon monoxide	
Methemoglobinemia	

HAART, highly active antiretroviral therapy; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

malnutrition, removal by dialysis, urinary losses with use of loop diuretics, increased metabolism as seen in sepsis, and during parenteral nutrition lacking in vitamins. Treatment with thiamine will rapidly lower the lactate levels.

Methanol. By itself, methanol is not toxic, but it is rapidly metabolized by alcohol dehydrogenase to formaldehyde, then formic acid (16,17). Accidental or intentional ingestion of windshield wiper fluid, glass cleaner, or contaminated beverages containing methanol can result in toxicity. As little as 15 ml of methanol can be fatal. Initially after ingestion, there is an osmolar gap (measured osmolality−calculated osmolality >15) caused by the alcohol, but as methanol is metabolized, the osmolar gap decreases and an AG acidosis appears (Figure 5). It is therefore important to calculate the osmolar gap in patients who are obtunded for unknown reasons, even in the absence of acidosis. Visual impairment and central nervous system depression are the hallmark signs of ingestion. Treatment consists of fomepizole or, if it is not available, ethanol (both competitive inhibitors of alcohol dehydrogenase) to prevent further breakdown of methanol to its toxic derivatives. Dialysis should be considered in the setting of methanol levels >500 mg/L, severe acidemia, coma, abnormalities in vision, kidney failure, or hemodynamic instability. Because clearance of methanol is greater using intermittent hemodialysis than with continuous modalities, unless otherwise contraindicated, this is the therapy of choice. Dialysis is typically discontinued when methanol levels become undetectable. Because of the association of methanol toxicity with intracerebral bleeding, some authorities recommend avoiding the use of heparin (18). Folic acid plays a role in formic acid oxidation, and although animal studies utilizing folate have shown a benefit, except for case reports, no human trials have been carried out (19). However, because administration of either folate or folinic acid is benign, it can be used as an adjunct therapy.

Ethylene Glycol. Ethylene glycol is a colorless, sweet liquid often used as antifreeze. Ingestion of 1–2 ml/kg is potentially lethal (17,20). Similar to methanol, the toxicity of ethylene glycol is related to its metabolism by alcohol dehydrogenase and aldehyde dehydrogenase, at first to glycolic acid and ultimately to oxalic acid. Patients present

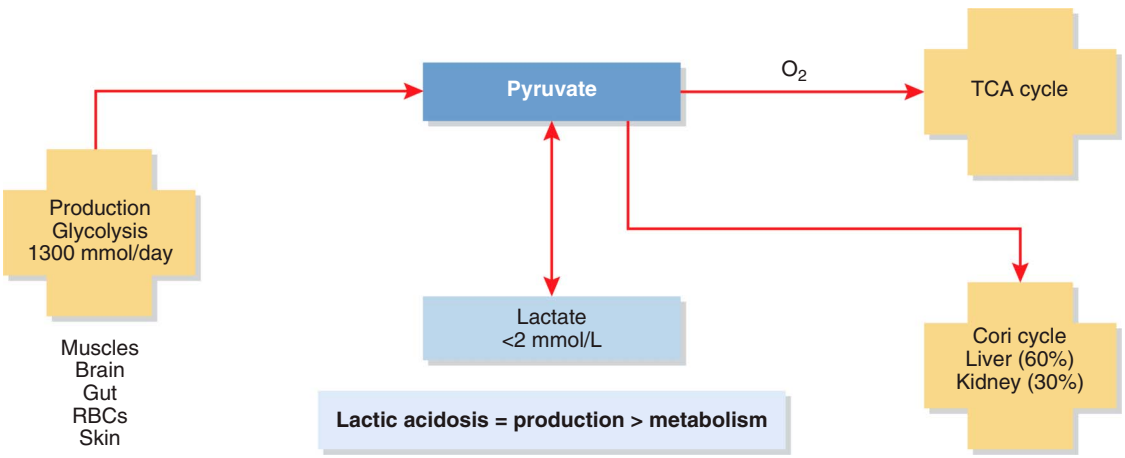

Figure 4. | Pyruvate, which is a byproduct of glycolysis, can enter the tricarboxcylic acid cycle where it is further metabolized to CO_2 and water, enter the Cori cycle to regenerate glucose, or, under anaerobic conditions, be hydrolyzed to lactate.

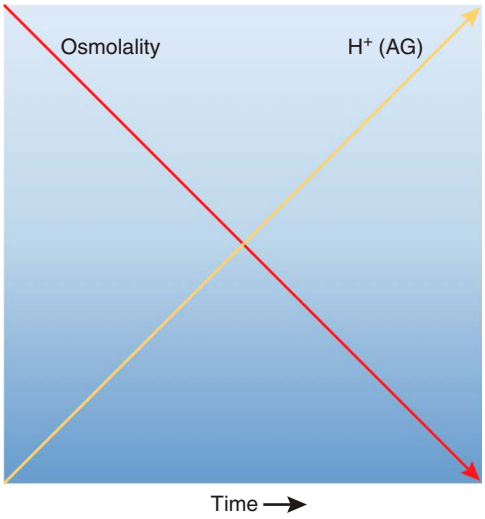

Figure 5. | Relationship between AG acidosis and osmolality after ingestion of a toxic alcohol. Initially, the alcohol produces an increase in osmolality without an increase in the AG. Metabolism of the alcohol reduces the osmolality and increases the AG.

with altered mental status and kidney failure. Labs will initially reveal an osmolar gap and an AG acidosis. As the ethylene glycol is oxidized, the osmolar gap will decrease as the AG worsens. Microscopic examination of the urine will often show calcium oxalate monohydrate crystals. It should be noted that some point-of-care analyzers may show a falsely elevated lactate level, due to interference by glycolate, one of the metabolites of ethylene glycol. Treatment consists of fomepizole or, if it is unavailable, ethanol and for patients that are severe, dialysis. Dialysis should also be considered when serum ethylene glycol levels are >50 mg/dl. Administration of pyridoxine and thiamine may be beneficial, both of which convert glyoxylic acid, a toxic metabolite of ethylene glycol, to nontoxic metabolites.

Propylene Glycol. Propylene glycol is used as a vehicle for numerous medications. Although considered safe, toxicity may result when used at increased doses (21,22). Propylene glycol is metabolized by alcohol dehydrogenase to both D- and L-lactic acid (23). Patients will exhibit both an AG acidosis and an osmolar gap. Because D-lactate is not measured by the usual assay, the AG is typically greater than can be explained by the measured lactate level. Most reported patients have been associated with infusions of lorazepam. Treatment consists of decreasing the dose of medication.

Pyroglutamic Acidosis (5-Oxoproline). Although most initial reports describing pyroglutamic acidosis were in chronic acetaminophen users with malnutrition, it has more recently been shown that patients who are septic have higher pyroglutamic acid and lower glutathione levels than healthy control (24,25). Thus, even acute use of acetaminophen may pose a risk of this AG acidosis. Because the ability of most clinical labs to measure pyroglutamic acid is lacking, this acidosis often goes unrecognized.

Ketoacidosis. Patients with ketoacidosis often require admission to the ICU. The two major causes of ketoacidosis seen in the ICU are diabetic and alcoholic. Although affecting different populations, the underlying pathophysiology of these disorders is similar: decreased insulin, increased counterregulatory hormones (glucagon, cortisol, catecholamines), and lipolysis, resulting in an increase in ketoacids, especially β-hydroxybutyrate acid.

Diabetic ketoacidosis (DKA) usually occurs in patients with type 1 diabetes, although ≤35% of the patients presenting with DKA have type 2 diabetes (26). It is important to rule out any underlying stressors, such as infections or myocardial ischemia. Patients usually present with nausea, abdominal pain, and signs of volume depletion. Labs reveal an AG acidosis, and due to both the lack of insulin and hypertonicity, hyperkalemia. It needs to be stressed, however, that although the potassium level may initially be elevated, total body potassium is almost always decreased, and treatment of the hyperglycemia will drive potassium back into cells and uncover the hypokalemia. Because ketone bodies are rapidly excreted in the urine, if volume contraction was avoided and GFR maintained, a concurrent hyperchloremic metabolic acidosis may also be present. Treatment is aimed at volume resuscitation, restoring adequate insulin levels to turn off ketogenesis or decrease hyperglycemia, and correct hypokalemia.

Patients with alcoholic ketoacidosis are typically chronic alcoholics, often with a recent episode of binge drinking (27). They present with nausea, vomiting, abdominal pain, and usually have discontinued nutrition 24–48 hours before admission. Labs reveal ketonemia and an AG acidosis. The acid-base status is often complex, with an AG acidosis, metabolic alkalosis from vomiting, and respiratory alkalosis from underlying liver disease. In fact, frank alkalemia may exist. In addition, labs will frequently reveal hypokalemia, hypomagnesemia, and hypophosphatemia. Although the glucose is usually normal or low, hyperglycemia may occur, making distinction from DKA difficult. Treatment consists of thiamine, correction of electrolytes abnormalities, dextrose if the glucose is normal, or insulin if hyperglycemic.

Salicylates. Salicylate toxicity presents classically as a mixed acid-base disorder with respiratory alkalosis due to stimulation of the respiratory center and an AG metabolic acidosis (28). Although in most patients with salicylate toxicity the AG is elevated, occasionally the AG may be negative. This occurs because salicylates can cause an artifactually elevated chloride level (psuedohyperchloremia) if the chloride selective electrode used for measurement is toward the end of its lifecycle. Symptoms of salicylate toxicity include tinnitus, nausea, and tachypnea. More severe patients may present with hyperthermia, coma, and pulmonary edema. Treatment consists of gastrointestinal decontamination with activated charcoal and alkalinization of the serum and urine to prevent salicylate entry into the central nervous system and to increase kidney excretion (29). Intravenous sodium bicarbonate should be infused aiming for a urine pH between 7.5 and 8. The presence of a respiratory alkalosis is not a contraindication to the use of sodium bicarbonate. Blood pH should be frequently monitored, however, to prevent severe alkalemia (pH >7.6). If the patient is obtunded, has pulmonary edema, or has a salicylate level >100 mg/dl, dialysis is indicated.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

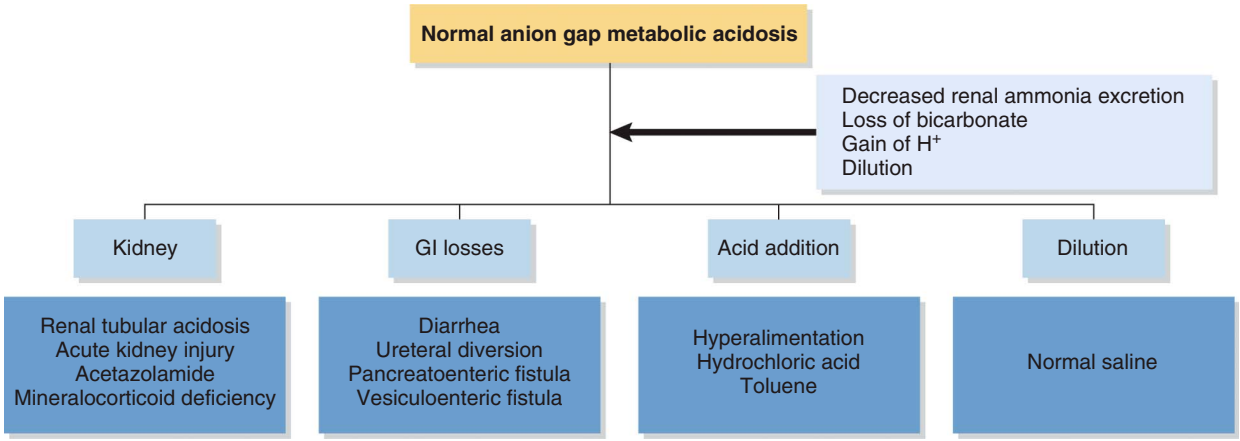

Figure 6. | **Etiology of a non–gap metabolic acidosis**.

Metformin. Elevated levels of metformin inhibit mitochondrial respiratory chain complex 1, which can result in the accumulation of lactic acid. Lactic acidosis associated with the use of metformin is uncommon, with an incidence between 3 and 10 per 10,000 patient-years. Because metformin is primarily secreted unmetabolized by the kidney, toxicity generally occurs in patients who have significant impairment of kidney function. Unfortunately, because it is difficult to promptly obtain metformin levels in patients on metformin who present with lactic acidosis, it is often necessary to assume the cause of the acidosis is secondary to metformin. If the lactate level is >20 mmol/L or pH ≤7.0, RRT should be initiated (30). Hemodialysis will not only clear the metformin, but will also improve the pH. Because the clearance of metformin is far greater with intermittent hemodialysis than with continuous modalities, if the patient is hemodynamically stable, this is the therapy of choice (30,31).

Normal Gap Metabolic Acidosis. Normal gap acidoses result from disorders of renal tubular H^+ transport, decreased kidney ammonia secretion, gastrointestinal and kidney losses of bicarbonate, dilution from excessive intravenous fluid administration, or addition of hydrochloric acid (HCL) (Figure 6).

Kidney Failure. Both acute and chronic kidney failure are common contributor to non-AG metabolic acidosis. This results from the inability of the kidney to generate adequate ammonia, thus limiting H^+ excretion.

Gastrointestinal Losses. Losses of pancreatic, biliary, or duodenal fluids, which are rich in bicarbonate, will cause a metabolic acidosis. Diarrhea is another cause of non-AG metabolic acidosis. Diarrhea not only diminishes colonic bicarbonate reabsorption, but also increases fecal loss.

Normal Saline. The infusion of copious quantities of normal saline frequently causes a non-AG metabolic acidosis. In two small studies, the infusion of 6 L of normal saline lowered the arterial pH to slightly below 7.35 (32,33). Although the pH of normal saline is approximately 5.47 because it contains no buffer, this represents a minimal amount of acid. It is therefore not the pH of normal saline, but the dilution of the serum bicarbonate without a change in pCO_2 that produces the acidemia (3,34).

Complications of Metabolic Acidosis

The presumed effects of metabolic acidemia are multiple; however, the severity and reversibility of dysfunction are largely dependent on the underlying cause and magnitude of the derangement (Table 4). Acidemia caused by sepsis has a much different outcome than a similar degree of acidosis seen in DKA, thus suggesting the cause of acidosis is more important than the actual pH. Although multiple studies have looked at the effects of acidemia on isolated cells and organs, little is known about the effects of changes in pH on whole-body physiology. This is especially true in patients who are critically ill. Although it intuitively makes sense that severe acidosis should have adverse effects *in*

Table 4. Purported effects of acidemia

Cardiovascular	Respiratory	Neurologic	Metabolic
Decreased cardiac contractility	Increased minute ventilation	Obtundation	Inhibition anaerobic metabolism
Decreased fibrillation threshold	Dyspnea	Increased cerebral blood flow	Hyperkalemia
Decreased sensitivity to catecholamines	Decreased diaphragmatic contractility	Decreased sympathetic discharge	Hyperphosphatemia
Decreased renal and hepatic blood flow	Respiratory muscle fatigue	Decreased cerebral metabolism	Increased protein metabolism
Centralization of blood volume			Increased metabolic rate

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

vivo, evidence clearly supporting this supposition is lacking (35–37).

Treatment of Metabolic Acidosis

The pH level requiring correction of acidemia is controversial. In patients with DKA, treatment with sodium bicarbonate has not been shown to improve outcomes, even when the pH is <7.0 (38). In lactic acidosis associated with sepsis, the parameters for treatment have been a moving target. We do not generally treat lactic acidosis unless the pH is <7.1. Unfortunately, treatment has not been shown to improve overall mortality (39,40). However, in a recent study, treatment with bicarbonate did improve mortality and decrease the need for RRT in a subset of patients with stage 2 or greater AKI and a median pH 7.15 (41). Therefore, in this population, the use of bicarbonate is recommended.

Administration of bicarbonate therapy can have several negative repercussions, including hypernatremia, hypocalcemia, increased lactate production, elevated mixed venous pCO_2, intracellular acidosis, and decreased cardiac output (40). Treatment of metabolic acidosis with sodium bicarbonate in the absence of severe metabolic acidosis with a pH of <7.15 not only lacks benefit, but may also be harmful (42,43). If used, it is recommended that sodium bicarbonate be infused slowly as an isotonic solution, with careful monitoring of ionized calcium.

Although other alkalinizing agents such as Tham (tromethamine) or Carbicarb have been suggested as alternate agents to treat acidemia, there are no data to support their benefit. Furthermore, neither are readily available. In addition to the use of bicarbonate to normalize pH, continuous RRT (CRRT) has been advocated to remove lactate. Unfortunately, in the presence of shock, lactic acid generation exceeds its clearance by CRRT (44,45). In addition, the removal of lactate, a base equivalent, may be harmful. Overall, the best therapy remains treatment of the underlying cause of the acidosis.

Respiratory Acidosis

Respiratory acidosis is caused by an increase in pCO_2 secondary to hypoventilation, increased dead space, or, less commonly, increased production. The most common cause of respiratory acidosis in the critical care setting is underlying chronic lung disease. This is best treated using noninvasive or invasive mechanical ventilation. An increasing cause of respiratory acidosis is the use of permissive hypercapnia in patients who have acute lung injury or acute respiratory distress syndrome. The use of permissive hypercapnia has become standard practice in patients with acute lung injury to reduce barotrauma. In addition to the prevention of barotrauma, there is also evidence that respiratory acidosis may have beneficial effects in attenuating the inflammatory cascade (46). Although bicarbonate is often used to ameliorate the acidemia associated with permissive hypercapnia, whether this is beneficial has not been clearly documented, and it may not only negate some of the benefits of this therapy but also be associated with adverse effects (47,48). Therefore, unless the pH is <7.1, we do not recommend the routine use of bicarbonate in patients with respiratory acidosis.

The use of CRRT for the removal of CO_2, however, may be beneficial. Significant CO_2 can be removed during continuous venovenous hemofiltration (49). In addition, there has been increasing interest in pairing extracorporeal CO_2 removal devices with continuous venovenous hemofiltration (50). Anecdotal reports using these devices showed a decreased pressor requirement and better management of acidemia (51,52). Thus, in patients requiring kidney replacement who have severe lung injury, the use of CO_2 removal devices in series with CRRT can be considered.

Metabolic Alkalosis

Metabolic alkalosis is the most common acid-base disorder seen in patients who are critically ill (53). Unlike metabolic acidosis, which is commonly present on admission to the ICU, metabolic alkalosis more frequently occurs after admission to the unit (53). Its etiology is most often secondary to the aggressive therapeutic interventions used to treat shock, acidemia, volume overload, severe coagulopathy, respiratory failure, bowel obstruction, and AKI (54).

Metabolic alkalosis results from the gain of base or the loss of acid. Most often this will result in an increase in pH and HCO_3. Because under normal conditions the kidney can excrete enormous quantities of HCO_3, the development of a metabolic alkalosis requires not only a phase during which HCO_3 is either added or acid is lost from the body, but also a maintenance phase during which the kidney is unable to excrete the HCO_3; for an in-depth review see Emmett (55). Although the underlying etiology can frequently be determined by the history and physical exam, if the cause of the metabolic alkalosis is not obvious, the etiology can be narrowed by measuring the urine Cl^- (Figure 7).

Etiology of Metabolic Alkalosis in the ICU

Nasogastric Suction or Vomiting. Secretion of hydrogen ions by gastric parietal cells *via* the H^+–K^+–ATPase produces an equal amount of HCO_3, which is secreted in the duodenum, where it combines with the protons in the gastric chyme to form water and CO_2. Thus, gastric acid secretion is a net neutral process. The parietal cells can secrete 140–160 meq/L of hydrogen ions. Nasogastric suction results in the loss of protons resulting in an increase in blood HCO_3 (Figure 8). If extracellular volume remains normal, HCO_3 will be rapidly excreted by the kidney. However, in the presence of volume depletion, less HCO_3 will be filtered at the glomerulus and volume-mediated increases in angiotensin II and aldosterone will increase both proximal and distal tubule HCO_3 reabsorption, maintaining the metabolic alkalosis. In addition, hypokalemia caused by an increase in urinary potassium excretion secondary to elevated aldosterone levels and increased distal tubule sodium reabsorption will exacerbate the alkalosis as potassium moves out of cells in exchange for H^+. The alkalosis will persist until the extracellular volume is restored to normal and potassium is repleted.

Contraction. Patients in the ICU, due to their underlying disease or because of resuscitation with intravenous fluids, are frequently volume overloaded. Aggressive diuresis

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

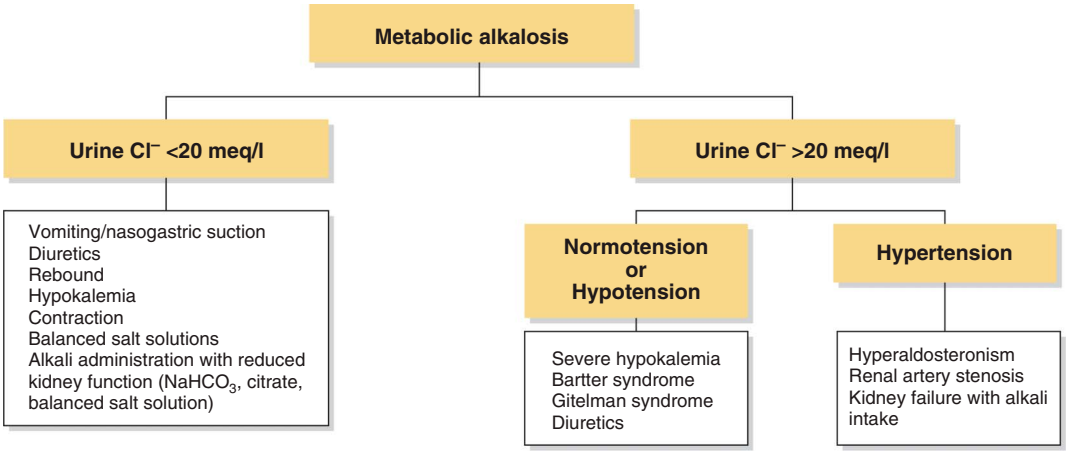

Figure 7. | **Etiology of a metabolic alkalosis**.

using loop or thiazide-type diuretics produces a urine that is almost free of HCO_3. Thus, the extracellular fluid contracts around a fixed HCO_3 content, raising the pH. In addition, the decrease in effective arterial blood volume stimulates neurohormonal effectors that promote bicarbonate reabsorption by the kidney. Furthermore, metabolic alkalosis is further exacerbated by hypokalemia from urinary losses of potassium.

Intravenous Fluids. Balanced salt solutions containing lactate, acetate, or gluconate (base equivalents) have the potential to be alkalinizing if used in excessive volume in patients with kidney dysfunction or in patients who are sodium depleted and unable to excrete a HCO_3 load.

Rebound. Often in an overzealous attempt to correct pH in patients with organic acidosis, a large amount of base is administered. When the process that created the excess organic acids (*e.g.*, sepsis, DKA) is terminated, the accompanying anions (lactate, hydroxybutyrate) are metabolized, consuming protons and raising the HCO_3 (56,57). If kidney function is abnormal or volume contraction is present, the excess HCO_3 is not excreted and a metabolic alkalosis ensues.

Citrate. Citrate is used as an anticoagulant in blood products, especially fresh frozen plasma and platelets. The administration of these products, or the transfusion of greater than 8–10 units of red cells can cause a metabolic alkalosis as citrate is converted to HCO_3 (58). Citrate is increasingly used as an anticoagulant during CRRT. Although between 30% and 60% of the administered citrate is cleared through the dialysis membrane, if the rate of citrate administration is excessive, blood flow is limited, or the membrane becomes clogged, citrate can accumulate, producing a metabolic alkalosis (59,60).

Post-Hypercapnic. In the presence of chronic hypercapnia, kidney hydrogen ion excretion and HCO_3 reabsorption by the kidney are increased to bring the pH back toward

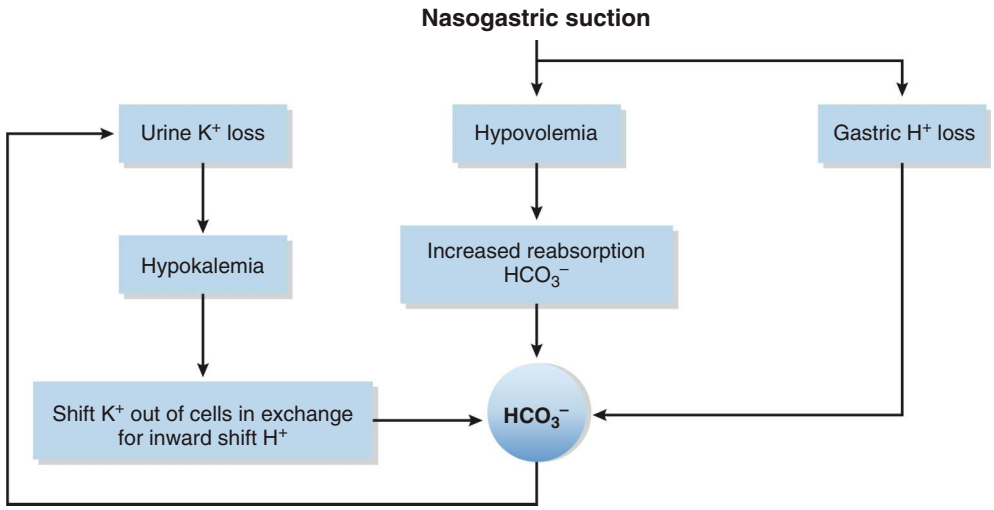

Figure 8. | **Etiology of a metabolic alkalosis associated with nasogastric suction.** Loss of gastric contents containing H^+ and Na^+ increases the serum HCO_3 and causes hypovolemia. Initially, the kidney excretes the excess HCO_3 along with K^+ causing hypokalemia. Potassium comes out of cells in exchange for the shift of H^+ into cells, worsening the alkalemia. Finally, hypovolemia activates neurohormonal mechanism that increases tubular reabsorption of HCO_3.

normal. If a patient with chronic CO_2 retention is placed on a ventilator and the pCO_2 is abruptly lowered to normal, the compensatory bicarbonate retention will be uncovered, creating frank alkalemia (61).

Hypokalemia. Hypokalemia causes metabolic alkalosis by a variety of mechanisms, including movement of K^+ out of cells in exchange for H^+, increased renal ammonia excretion, and activation of H^+K^+ATPase in the cortical collecting duct.

Complications of Metabolic Alkalosis

Studies have shown that metabolic alkalosis is associated with a higher morbidity and mortality (54,62). In these studies, as pH increased, so did mortality. It is unclear, however, whether the increase in mortality is due to the alkalemia itself or the underlying conditions responsible for the change in pH. The association between alkalemia and mortality appeared in the older literature and was not adjusted for other morbidities (54,62). In a more recent retrospective study in patients with sepsis, after adjustment for age, Simplified Acute Physiology Score III and AKI, no association between alkalosis and mortality was noted (63). This study, however, did show that alkalemia was associated with longer ICU length of stay.

It is clearly established that alkalemia causes a decrease in ionized calcium and an increase in pCO_2. Many of the neurologic symptoms associated with alkalemia such as paresthesia, tetany, muscle spasm, and seizures are secondary to hypocalcemia. In response to the increase in pH, minute ventilation is suppressed with a subsequent increase in PCO_2, which brings the pH back toward normal. This decrease in respiratory drive may make it more difficult to extubate patients who are ventilated. The increase in PCO_2 also causes a fall in alveolar oxygen content and decreased oxygen saturation. This is compounded by a shift in the oxyhemoglobin dissociation curve toward the left, decreasing the release of oxygen from hemoglobin. This, however, is mitigated by an increase in 2,3-diphosphoglycerate induced by alkalemia. Increases in both supraventricular and ventricular arrhythmias have been reported with alkalemia, although these cardiac effects may be secondary to hypokalemia and hypomagnesemia, which are frequently present in patients with alkalosis rather than the alkalemia.

Treatment of Metabolic Alkalosis

The treatment of metabolic alkalosis depends on the underlying etiology. The pH level at which treatment should be initiated is not clearly established and is left up to the individual clinician. Because morbidity associated with alkalemia may increase above a pH of 7.55, this is a reasonable target value to choose. Because of the effects of hypokalemia on both H^+ movement into cells and the kidney reabsorption of HCO_3, hypokalemia should be aggressively treated. Whenever possible, volume depletion should be addressed and corrected.

In patients with metabolic alkalosis from nasogastric suction, blocking acid secretion with proton pump inhibitors can decrease but not eliminate the loss of H^+ (64). In addition, potassium and chloride repletion will enable the kidney to excrete the excess HCO_3.

When alkalosis is secondary to volume contraction from diuretics, it is often not desirable to re-expand the extracellular space. In those patients, the administration of acetazolamide, a carbonic anhydrase inhibitor, will increase renal HCO_3 excretion, improving the pH (65). It is important to prevent hypokalemia when using this medication. If this is unsuccessful and the pH is >7.55 with a HCO_3 >35 meq/L, HCL if available can be infused *via* a central vein (66); 0.1 N HCL in sterile water will supply 100 meq/L H^+. This can be infused at 100 ml/h. Assuming the volume of distribution of HCO_3 is approximately equal to 50% of lean body weight, the amount of HCL needed to bring the HCO_3 to 35 meq/L or lower can be calculated. In patients with kidney failure and severe alkalemia, hemodialysis can be considered.

When metabolic alkalosis is secondary to overventilation, the first step would be to decrease minute ventilation by decreasing the respiratory rate or tidal volume. In addition, hypokalemia and volume depletion should be corrected. Although acetazolamide will improve pH and lower the pCO_2, studies have not demonstrated a decrease in ventilator days (67).

Respiratory Alkalosis

Respiratory alkalosis is frequently encountered in the ICU. Many of the disorders found in patients who are critically ill are associated with hyperventilation. One of the earliest signs of sepsis is an increase in the respiratory rate. Patients with cirrhosis uniformly have an increase in respiratory rate, presumed secondary to elevated levels of progesterone. Hypoxia stimulated increase in the respiratory drive from heart failure, acute asthma, pulmonary embolism, and interstitial lung disease are all associated with hypocarbia. In addition, the anxiety related to being in the ICU itself can cause a respiratory alkalosis. Inadequate sedation and pain control in patients on mechanical ventilation is often associated with a respiratory alkalosis. Another cause of respiratory alkalosis seen in the ICU occurs with aspirin overdose. In addition to causing metabolic acidosis, salicylates directly stimulate the respiratory center to cause hyperventilation in a dose-dependent manner.

Mixed Acid-Base Disorders

Because of the complexity of patients who are critically ill, it is not unusual for them to manifest double or even triple acid-base disturbances. If a systematic approach to acid-base disorders is used on all patients, the clinician should easily be able to identify the underlying disorders.

Acid-base disturbances are common in the ICU. This brief review highlights the common causes that disrupt normal acid-base homeostasis. It is important to recognize their presence, understand the underlying cause of these disturbances, and be able to therapeutically intervene when appropriate.

Disclosures

A. Achanti reports having consultancy agreements with Chinook Therapeutics and Ad-board for atrasentan and reports receiving

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024

research funding from Cure Glomerulonephropathy Kaneka Medical America LLC sub-I LDL apheresis for FSGS and the Omeros IgA trial. H.M. Szerlip reports having consultancy agreements with Amarin, AstraZeneca, Echonous, and Relypsa; having an ownership interest in Amgen, Biomarin, Gilead, Merck, and Pfizer; receiving research funding from Akebia, Aurinnia, Bayer, Boehringer Ingelheim, and Fibrogen; receiving honoraria from AstraZeneca, GlaxoSmithKlein, LaJolla Pharmaceuticals, and Triceda; serving on the Acute Care Committee of the National Board of Medical Examiners, Medical Knowledge Self-Assessment Program 19 committee of the American College of Physicians, and as an author for UpToDate; receiving honoraria as a speaker for AstraZeneca, GSK, LaJolla, and Tricida; and having other interests or relationships with American College of Physicians, American Society of Nephrology, and National Kidney Foundation.

Funding

None.

Acknowledgments

Louise Cochran proofed and edited the manuscript.

Author Contributions

H.M. Szerlip provided supervision, and A. Achanti and H.M. Szerlip wrote the original draft and reviewed and edited the manuscript.

References

1. Al-Jaghbeer M, Kellum JA: Acid-base disturbances in intensive care patients: Etiology, pathophysiology and treatment. *Nephrol Dial Transplant* 30: 1104–1111, 2015
2. Stewart PA: Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 61: 1444–1461, 1983
3. Masevicius FD, Dubin A: Has Stewart approach improved our ability to diagnose acid-base disorders in critically ill patients? *World J Crit Care Med* 4: 62–70, 2015
4. Kurtz I, Kraut J, Ornekian V, Nguyen MK: Acid-base analysis: A critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol* 294: F1009–F1031, 2008
5. Chong WH, Saha BK, Medarov BI: Comparing central venous blood gas to arterial blood gas and determining its utility in critically ill patients: Narrative review. *Anesth Analg* 133: 374–378, 2021
6. Schrauben SJ, Negoianu D, Costa C, Cohen RM, Goldfarb S, Fuchs BD, Berns JS: Accuracy of acid-base diagnoses using the central venous blood gas in the medical intensive care unit. *Nephron* 139: 293–298, 2018
7. Figge J, Jabor A, Kazda A, Fencl V: Anion gap and hypoalbuminemia. *Crit Care Med* 26: 1807–1810, 1998
8. Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA, Schrier RW: Diagnostic importance of an increased serum anion gap. *N Engl J Med* 303: 854–858, 1980
9. Mehta AN, Emmett JB, Emmett M: GOLD MARK: An anion gap mnemonic for the 21st century. *Lancet* 372: 892, 2008
10. Fall PJ, Szerlip HM: Lactic acidosis: From sour milk to septic shock. *J Intensive Care Med* 20: 255–271, 2005
11. Villar J, Short JH, Lighthall G: Lactate predicts both short- and long-term mortality in patients with and without sepsis. *Infect Dis (Auckl)* 12: 1178633719862776, 2019
12. Chawla LS, Jagasia D, Abell LM, Seneff MG, Egan M, Danino N, Nguyen A, Ally M, Kimmel PL, Junker C: Anion gap, anion gap corrected for albumin, and base deficit fail to accurately diagnose clinically significant hyperlactatemia in critically ill patients. *J Intensive Care Med* 23: 122–127, 2008
13. Dinh CH, Ng R, Grandinetti A, Joffe A, Chow DC: Correcting the anion gap for hypoalbuminaemia does not improve detection of hyperlactataemia. *Emerg Med J* 23: 627–629, 2006
14. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP: Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. *Crit Care Med* 18: 275–277, 1990
15. Attaluri P, Castillo A, Edriss H, Nugent K: Thiamine deficiency: An important consideration in critically ill patients. *Am J Med Sci* 356: 382–390, 2018
16. Ashurst JV, Nappe TM: *Methanol Toxicity*, Treasure Island, FL, StatPearls, 2022
17. Kraut JA, Mullins ME: Toxic alcohols. *N Engl J Med* 378: 270–280, 2018
18. Permpalung N, Cheungpasitporn W, Chongnarungsin D, Hodgdon TM: Bilateral putaminal hemorrhages: Serious complication of methanol intoxication. *N Am J Med Sci* 5: 623–624, 2013
19. Theobald J, Lim C: Folate as an adjuvant therapy in methanol poisoning. *Nutr Clin Pract* 34: 521–527, 2019
20. Iqbal A, Glagola JJ, Nappe TM: *Ethylene Glycol Toxicity*, Treasure Island, FL, StatPearls, 2022
21. Wilson KC, Reardon C, Theodore AC, Farber HW: Propylene glycol toxicity: A severe iatrogenic illness in ICU patients receiving IV benzodiazepines: A case series and prospective, observational pilot study. *Chest* 128: 1674–1681, 2005
22. Zosel A, Egelhoff E, Heard K: Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy* 30: 219, 2010
23. Jorens PG, Demey HE, Schepens PJ, Coucke V, Verpooten GA, Couttenye MM, Van Hoof V: Unusual D-lactic acid acidosis from propylene glycol metabolism in overdose. *J Toxicol Clin Toxicol* 42: 163–169, 2004
24. Emmett M: Acetaminophen toxicity and 5-oxoproline (pyroglutamic acid): A tale of two cycles, one an ATP-depleting futile cycle and the other a useful cycle. *Clin J Am Soc Nephrol* 9: 191–200, 2014
25. Gamarra Y, Santiago FC, Molina-López J, Castaño J, Herrera-Quintana L, Domínguez Á, Planells E: Pyroglutamic acidosis by glutathione regeneration blockage in critical patients with septic shock. *Crit Care* 23: 162, 2019
26. Nyenwe EA, Kitabchi AE: The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism* 65: 507–521, 2016
27. Long B, Lentz S, Gottlieb M: Alcoholic ketoacidosis: Etiologies, evaluation, and management. *J Emerg Med* 61: 658–665, 2021
28. Gabow PA, Anderson RJ, Potts DE, Schrier RW: Acid-base disturbances in the salicylate-intoxicated adult. *Arch Intern Med* 138: 1481–1484, 1978
29. Vree TB, Van Ewijk-Beneken Kolmer EW, Verwey-Van Wissen CP, Hekster YA: Effect of urinary pH on the pharmacokinetics of salicylic acid, with its glycine and glucuronide conjugates in human. *Int J Clin Pharmacol Ther* 32: 550–558, 1994
30. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M; Extracorporeal Treatments in Poisoning Workgroup: Extracorporeal treatment for metformin poisoning: Systematic review and recommendations from the extracorporeal treatments in poisoning workgroup. *Crit Care Med* 43: 1716–1730, 2015
31. Lemyze M, Baudry JF, Collet F, Guinard N: Life threatening lactic acidosis. *BMJ* 340: c857, 2010
32. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 90: 1265–1270, 1999
33. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR: Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: An outcome study. *Anesth Analg* 93: 817–822, 2001
34. Reddi BA: Why is saline so acidic (and does it really matter?). *Int J Med Sci* 10: 747–750, 2013
35. Cooper DJ, Walley KR, Wiggs BR, Russell JA: Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Ann Intern Med* 112: 492–498, 1990
36. Jia S, Kumar P: Con: Metabolic acidosis should not be corrected with sodium bicarbonate in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 36: 619–621, 2022
37. George AK, Shih A, Regan TJ: Effect of acute ketoacidosis on the myocardium in diabetes. *Am J Med Sci* 311: 61–64, 1996

38. Chua HR, Schneider A, Bellomo R: Bicarbonate in diabetic ketoacidosis: A systematic review. *Ann Intensive Care* 1: 23, 2011
39. Lo KB, Garvia V, Stempel JM, Ram P, Rangaswami J: Bicarbonate use and mortality outcome among critically ill patients with metabolic acidosis: A meta analysis. *Heart Lung* 49: 167–174, 2020
40. Rudnick MR, Blair GJ, Kuschner WG, Barr J: Lactic acidosis and the role of sodium bicarbonate: A narrative opinion. *Shock* 53: 528–536, 2020
41. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandière M, Asehnoune K, Dellamonica J, Velly L, Abback PS, de Jong A, Brunot V, Belafia F, Roquilly A, Chanques G, Muller L, Constantin JM, Bertet H, Klouche K, Molinari N, Jung B; BICAR-ICU Study Group: Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): A multicentre, open-label, randomised controlled, phase 3 trial. *Lancet* 392: 31–40, 2018
42. Kim HJ, Son YK, An WS: Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: A retrospective analysis. *PLoS One* 8: e65283, 2013
43. Rachoin JS, Weisberg LS, McFadden CB: Treatment of lactic acidosis: Appropriate confusion. *J Hosp Med* 5: E1–E7, 2010
44. Cheungpasitporn W, Zand L, Dillon JJ, Qian Q, Leung N: Lactate clearance and metabolic aspects of continuous high-volume hemofiltration. *Clin Kidney J* 8: 374–377, 2015
45. Levraut J, Ciebiera JP, Jambou P, Ichai C, Labib Y, Grimaud D: Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. *Crit Care Med* 25: 58–62, 1997
46. Ni Chonghaile M, Higgins B, Laffey JG: Permissive hypercapnia: Role in protective lung ventilatory strategies. *Curr Opin Crit Care* 11: 56–62, 2005
47. Chand R, Swenson ER, Goldfarb DS: Sodium bicarbonate therapy for acute respiratory acidosis. *Curr Opin Nephrol Hypertens* 30: 223–230, 2021
48. Adrogué HJ, Madias NE: Alkali therapy for respiratory acidosis: A medical controversy. *Am J Kidney Dis* 75: 265–271, 2020
49. Jonckheer J, Spapen H, Debain A, Demol J, Diltoer M, Costa O, Lanckmans K, Oshima T, Honoré PM, Malbrain M, De Waele E: CO_2 and O_2 removal during continuous veno-venous hemofiltration: A pilot study. *BMC Nephrol* 20: 222, 2019
50. Jacobs R, Sablon A, Spapen H: Extracorporeal carbon dioxide removal during continuous renal replacement therapy as adjunctive therapy. *Respir Care* 65: 517–524, 2020
51. Forster C, Schriewer J, John S, Eckardt KU, Willam C: Low-flow CO_2 removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. *Crit Care* 17: R154, 2013
52. Grant AA, Hart VJ, Lineen EB, Forsberg BC, Klima A, Mirsaeidi M, Schulman IH, Badiye A, Vianna RM, Patel A, Loebe M, Ghodsizad A: Rescue therapy for hypercapnia due to high PEEP mechanical ventilation in patients with ARDS and renal failure. *Artif Organs* 43: 599–604, 2019
53. Maehle K, Haug B, Flaatten H, Nielsen E: Metabolic alkalosis is the most common acid-base disorder in ICU patients. *Crit Care* 18: 420, 2014
54. Webster NR, Kulkarni V: Metabolic alkalosis in the critically ill. *Crit Rev Clin Lab Sci* 36: 497–510, 1999
55. Emmett M: Metabolic alkalosis: A brief pathophysiologic review. *Clin J Am Soc Nephrol* 15: 1848–1856, 2020
56. Whang R: "Bicarbonate overshot": An indication for acetazolamide therapy. *South Med J* 68: 733–734, 1975
57. Robin ED: Dynamic aspects of metabolic acid base disturbances: Phenformin lactic acidosis with alkaline overshoot. *Trans Assoc Am Physicians* 85: 317–324, 1972
58. Li K, Xu Y: Citrate metabolism in blood transfusions and its relationship due to metabolic alkalosis and respiratory acidosis. *Int J Clin Exp Med* 8: 6578–6584, 2015
59. Kovvuru K, Velez JCQ: Complications associated with continuous renal replacement therapy. *Semin Dial* 34: 489–494, 2021
60. Schneider AG, Journois D, Rimmelé T: Complications of regional citrate anticoagulation: Accumulation or overload? *Crit Care* 21: 281, 2017
61. Banga A, Khilnani GC: Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. *COPD* 6: 437–440, 2009
62. Anderson LE, Henrich WL: Alkalemia-associated morbidity and mortality in medical and surgical patients. *South Med J* 80: 729–733, 1987
63. Kreü S, Jazrawi A, Miller J, Baigi A, Chew M: Alkalosis in critically ill patients with severe sepsis and septic shock. *PLoS One* 12: e0168563, 2017
64. Eiro M, Katoh T, Watanabe T: Use of a proton-pump inhibitor for metabolic disturbances associated with anorexia nervosa. *N Engl J Med* 346: 140, 2002
65. Marik PE, Kussman BD, Lipman J, Kraus P: Acetazolamide in the treatment of metabolic alkalosis in critically ill patients. *Heart Lung* 20: 455–459, 1991
66. Guffey JD, Haas CE, Crowley A, Connor KA, Kaufman DC: Hydrochloric acid infusion for the treatment of metabolic alkalosis in surgical intensive care unit patients. *Ann Pharmacother* 52: 522–526, 2018
67. Faisy C, Mokline A, Sanchez O, Tadié JM, Fagon JY: Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive Care Med* 36: 859–863, 2010

Published online ahead of print. Publication date available at www.cjasn.org.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 08/18/2024